

Surveillance for Adverse Events following Immunization from 2008 to 2011 in Zhejiang Province, China

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This study summarizes passive surveillance data for adverse events following immunization (AEFI) reported to the National AEFI Surveillance System (NASS) in Zhejiang province and describes reporting trends from 2008 to 2011. AEFI reporting rates were calculated using denominator data from the Individual Immunization Information System and the Zhejiang provincial Bureau of Statistics. A total of 6,265 AEFI records were reported; the overall reporting rate was 9.2 per 100,000 doses. There were two peaks of reporting rates, which were associated mainly with the introduction of the pandemic H1N1 influenza virus vaccine (pH1N1) in 2009 and the measles-mumps vaccine (MM) campaign in 2010. The majority of the AEFI described nonserious events. Fifteen deaths were recorded, but only one was possibly related to immunization. The most frequently reported reactions were fever and injection site reaction. Vaccines distributed in Zhejiang province have proven to be generally safe. The data on AEFI surveillance provide a reference point for ongoing reporting of trends and illustrate the value of the NASS database as a surveillance tool for monitoring of AEFI.

During the last decade, rising concerns about vaccine and immunization safety have emerged among the medical community as well as the public (1). These concerns have led to decreasing vaccine rates in some areas, mainly affecting the coverage of the measles-containing vaccine (MCV). One way to maintain the public confidence in the Expand Program of Immunization (EPI) is to collect data on and assess adverse events following immunization (AEFI) (2). Careful and continuous analysis of such data allows a critical evaluation of the actual AEFI surveillance system. In this respect, unusual increases in rates of previously reported AEFI are as important to be detected, as are hitherto unknown AEFI (signal detection) until now. Monitoring and evaluation of vaccine safety therefore are an integral part of the EPI.

Zhejiang is a developed province with a large population of 80 million people in eastern areas of China. Since 1978, Zhejiang province initiated the EPI and administered more than 20 million doses of vaccines each year according to the immunization schedule recommended by Ministry of Health (MoH) of China. In 2008, Zhejiang joined in the national AEFI surveillance system. On the basis of guidelines for AEFI surveillance that were issued by the MoH of China (3), all AEFI are mandatorily reported and should be reported by the county or municipal Center for Disease Control and Prevention (CDC), health centers, physicians, vaccine manufacturers, and members of the public if (i) the AEFI occurred with a reasonable temporal association (i.e., within 3 months after immunization), (ii) no other plausible cause explained the event, and (iii) the AEFI fulfilled one or more of the following criteria: it is serious, previously unknown to occur after immunization, or the main cause for a physician visit.

The goal of this study was a detailed analysis of all AEFI reported in Zhejiang province between 2008 and 2011.

MATERIALS AND METHODS

Data collection. Each reported AEFI should be investigated by the county or municipal CDC. Reports of AEFI should contain the following information in a standardized fashion: date of report, age and sex of patient, kind and lot of suspect vaccine(s), description of the AEFI, time interval after immunization, duration of the event, final outcome of AEFI, and any other additional remarks from the reporter. All the data should be entered

into the online National AEFI Surveillance System (NASS) (<http://219.141.175.204/>), which was established on the basis of World Health Organization (WHO) guidelines. A provincial expert committee is organized to review all the reported AEFIs. This expert committee is composed of independent medical experts who have expertise in areas of importance to the evaluation of vaccine safety.

According to the immunization schedule of the EPI recommended by the Chinese MoH (4), the database provided by the NASS was subdivided by the following suspected vaccine categories: *Mycobacterium bovis* bacillus Calmette-Guérin live attenuated vaccine (BCG); diphtheria-tetanus combined vaccine, adolescent and adult formulation (DT); diphtheria-tetanus-pertussis combined vaccine, pediatric formulation (DTP); oral poliovirus live attenuated vaccine (OPV); measles-mumps-rubella combined live attenuated vaccine (MMR); measles-rubella combined live attenuated vaccine (MR); measles-mumps combined live attenuated vaccine (MM); hepatitis B virus vaccine (HepB); hepatitis A virus vaccine (HepA); meningococcal polysaccharide vaccine type a (MenV-a); meningococcal polysaccharide vaccine types a and c (MenV-ac); Japanese encephalitis virus live attenuated vaccine (JEV); pandemic H1N1 influenza A virus vaccine (pH1N1); and other vaccines.

Average annual population data were obtained from the Zhejiang provincial Bureau of Statistics (5), and the yearly number of distributed doses of various vaccines in Zhejiang province during the study period was obtained from the online individual immunization information system of Zhejiang province, which was established in 2005. These data allowed an estimation of reporting rates.

Causality assessment. We attempted to assess each single report regarding its causal link to the administered vaccine(s) by use of the following categories based on modified (modifications indicated in parentheses below) WHO recommendations on causality assessment of AEFI (6): unclassifiable, AEFI with insufficient information to permit assessment and identification of the cause; unrelated, AEFI with an incompatible time

Received 20 September 2012 Returned for modification 5 November 2012

Accepted 2 December 2012

Published ahead of print 12 December 2012

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doi:10.1128/CVI.00541-12

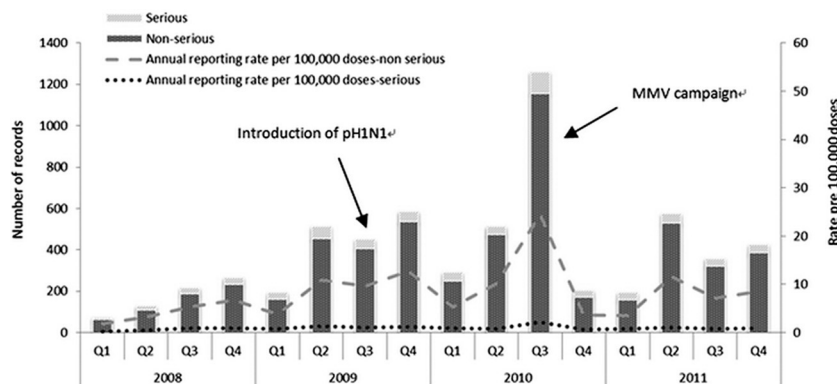


FIG 1 AEFI reports in the NASS database, 2008 to 2011, by quarter of onset of AEFI.

relationship (live attenuated vaccine >30 days and inactivated vaccines >7 days after immunization) and which could be explained by underlying disease or other drugs or chemicals; unlikely, unknown AEFI (not mentioned in the literature) but in a plausible time interval (live attenuated vaccine 0 to 30 days and inactivated vaccine 0 to 7 days after immunization) (the WHO definition is an AEFI where the time relationship to vaccine administration makes a causal relation improbable but which could be plausibly explained by underlying disease or other drugs or chemicals); possible, AEFI with a reasonable time relationship to vaccine administration but which could also be explained by concurrent disease or other drugs or chemicals; probable, AEFI with a reasonable time relationship to vaccine administration and which is unlikely to be attributed to concurrent disease or other drugs or chemicals (and local reactions at the injection site with an unknown time relationship to vaccine administration); and very likely or certain, AEFI with a reasonable time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.

Assessment of severity and reactions. All AEFI were assessed as non-serious or serious and further subdivided into the following categories of severity including the definition for “serious” AEFI proposed by the WHO (7): nonserious (mild severity), with no intervention necessary; nonserious (moderate severity), with medication given or physician visit or event interfering with daily activities or loss of working hours; and serious (severe), with any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, or persistent or significant disability/incapacity or is life threatening.

Each AEFI record lists several symptoms, signs, and/or diagnoses that have been recoded by municipal- and/or county-level CDC staff from the reporter’s description into standardized terms according to guidelines for the identification of AEFI issued by the MoH of China in 2008 (8). AEFI reports of suspected anaphylaxis were reviewed by the provincial expert committee and classified using the Brighton Collaboration case definitions.

Data analysis. For statistical analysis, we organized the database as an Excel file (Microsoft Office Excel 2010). Reporting rates were calculated by use of the Excel program. Reporting rates of AEFI (per 100,000 distributed doses) were analyzed by vaccine categories and reaction categories. In cases of coadministration of two or more vaccines in an individual, we attributed the reported AEFI to the vaccine which most likely caused the event. We categorized patients by the following age groups: ~0 to 1 year, ~1 to 5 years, ~5 to 7 years, ~7 to 20 years, and ~20 to 65 years.

RESULTS

The NASS included a total of 6,265 AEFI records for which the date of AEFI occurred between 1 January 2008 and 31 December 2011. Of these, 539 records were related to pH1N1, which was introduced in October 2009, and 792 records were related to MM,

which was used in the campaign for measles elimination in September 2010. A total of 36.7% of AEFI ($n = 1,588$) were reported by health centers, 58% ($n = 3,633$) were reported by county-level CDC, 4.5% ($n = 283$) were reported by municipal-level CDC, and 0.8% ($n = 51$) were reported by vaccine manufacturers.

Reporting trends. The overall AEFI reporting rate for the study period was 9.2 per 100,000 doses. The highest annual reporting rate was 12/100,000 doses in 2010, while the lowest one was 4.9/100,000 doses in 2004. Figure 1 shows the sharp increase in AEFI reporting rates in the last quarter of 2009 due to the introduction of pH1N1 and in the third quarter of 2010 due to the province-wide MM campaign. Reporting rates usually increased with the commencement of a new vaccination program and then stabilized at a lower level. The usual seasonal pattern of AEFI reporting, with more records in the second half of the year, was apparent in every year. The average reporting rate for the first half of the year was 7.1/100,000 doses, and that for the second half of the year was 10.8/100,000 doses.

Age distribution. The highest AEFI reporting rate was for infants <1 year of age (85.2 per 100,000 population on average), who received the largest number of vaccines (Fig. 2). Compared with the average rates of other years, there were remarkable increases in AEFI reporting rates for individuals ~7 to 65 years of age (357.9% increase, from 0.76 to 3.48 per 100,000 population) in 2009 and for individuals ~0 to 5 years of age (41.2% increase, from 98.1 to 138.4 per 100,000 population) in 2010.

Geographical distribution. All municipalities reported AEFI during the study period. Most AEFI ($n = 3,195$; 50.9%) had been reported by Hangzhou and Ningbo. Quzhou had the highest reporting rate (30.5 per 100,000 doses), followed by Hangzhou and Ningbo (17.0 and 16.4 per 100,000 doses, respectively), while Huzhou had the lowest rate (3.0 per 100,000 doses) (Table 1).

Causality assessment. Each report was assessed by its possible causal relationship to the preceding immunization(s). Of the total AEFI reports, no causal relationship was found for 3,257 reports (51.9%), whereas a causal relationship was unlikely for 2,237 reports (35.7%), possible for 415 reports (6.6%), probable for 199 reports (3.2%), and very likely or certain for 146 reports (2.3%) (Table 1).

Outcomes and seriousness assessment. Of the total AEFI records, 5,223 (83.4%) were nonserious (4,518 were mild and 705 were moderate). A total of 652 records (10.4%) were serious and severe, including 15 deaths, 495 hospitalizations, 27 events leading

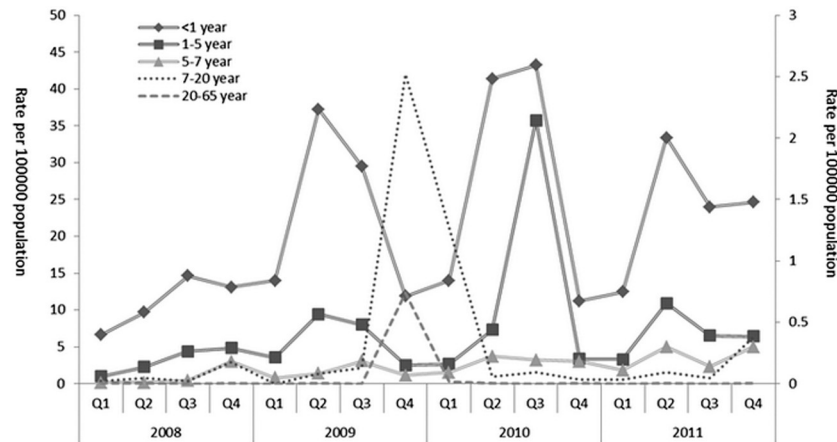


FIG 2 AEFI per 100,000 population in the NASS database, 2008 to 2011, by age group and onset of AEFI.

to permanent disabilities, and 115 life-threatening events. A total of 390 records (6.2%) without sufficient information for outcomes and seriousness assessment were classified as missing data. Only 72 (11.0%) serious records were considered to be certainly or probably related to immunization. A total of 599 (91.9%) serious records occurred for patients <7 years of age, and 53 (8.1%) occurred for patients ≥7 years of age (Table 2).

There were 15 (0.2%) deaths among 6,265 reported AEFI records (0.02 reported deaths per 100,000 doses). All cases were infants (<1 year of age), and 9 were female.

Five deaths occurred in association with HepB immunization in infants (all were <3 months of age), and the time interval between immunization and death varied between 0 and 3 days without any cluster. Four of these infant deaths were reported as “sudden infant death syndrome” (SIDS). The other infant died from asphyxia. None of these cases were assessed to be causally related to immunization based on data in the literature disproving a causal relationship between sudden unexpected death in infants and immunization.

TABLE 1 AEFI per 100,000 doses from the NASS database, 2008 to 2011, by municipality

Municipality	No. of AEFI records	% of AEFI records	Avg annual reporting rate per 100,000 doses ^a			
			Overall	Very likely or certain causality	Probable causality	Serious outcome ^b
Hangzhou	1,652	26.4	17.0	0.25	0.29	1.4
Ningbo	1,543	24.6	16.4	0.21	0.33	1.0
Wenzhou	480	7.7	3.9	0.08	0.11	0.4
Jiaxing	397	6.3	8.9	0.18	0.29	1.4
Huzhou	101	1.6	3.3	0.16	0.26	0.8
Shaoxing	204	3.3	4.0	0.26	0.36	0.5
Jinhua	332	5.3	3.9	0.35	0.42	1.2
Quzhou	594	9.5	30.5	0.13	0.27	2.2
Zhoushan	101	1.6	10.9	0.32	0.46	1.5
Taizhou	463	7.4	4.9	0.26	0.35	0.9
Lishui	398	6.4	13.0	0.18	0.29	0.3
Total	6,265	100.0	9.2	0.21	0.29	1.0

^a Average annual rates per 100,000 doses calculated using total vaccine doses estimated for 2008 to 2011.

^b AEFI records defined as serious (i.e., recovery with sequelae, hospitalization, life threatening, or death).

Four deaths followed 0 to 95 days after BCG immunization. Of these, three were reported as a coincidental event, and all of them were investigated and classified as not related to immunization. The other patient, with underlying high immunoglobulin E syndrome (HIES), was diagnosed as having disseminated BCG infection, assessed as possibly related to immunization based on data in the literature proving a possible causal relationship between disseminated BCG infection and vaccination for an HIES patient.

Six further deaths (including 3 deaths associated with DTP, 2 deaths associated with OPV, and 1 associated with MR) were assessed to be unrelated to the immunization because of other plausible causes for death: 3 infants died from pneumonia with consecutive multiorgan failure, 2 died from asphyxia, and 1 died in a traffic accident.

Vaccines. Nineteen different vaccines were included in the 6,265 AEFI records received between 2008 and 2011 (Table 3). The most frequently reported individual vaccine was DTP, with 1,833 records (30.0%), followed by MM (901;14.4%), pH1N1 (539; 8.6%), MR (459; 7.3%), and DT (327; 5.2%). The 23-valent pneumococcal polysaccharide vaccine (23vPPV), the 7-valent pneu-

TABLE 2 Outcomes of AEFI in the NASS database, 2008 to 2011

Outcome	AEFI records		Certain/probable causality rating		Age group			
	No.	% ^a	No.	% ^b	<7 years		≥7 years	
Serious	652	10.4	72	11.0	599	91.9	53	8.1
Recovered with sequelae	5		0		5	100.0	0	0.0
Hospital treatment, admission	495		61		466	94.1	29	5.9
Life-threatening event	137		10		101	73.7	36	26.3
Death	15		1		15	100.0	0	0.0
Nonserious	5,223	83.4	257	4.9	4,637	88.8	586	11.2
Not known (missing data)	390	6.2	16	4.1	371	95.1	19	4.9
Total	6,265		345	5.5	5,607	89.5	658	10.5

^a Percentages relate to the total number of AEFI records ($n = 6,265$).

^b Percentages relate to the number of AEFI records with the specific outcome (e.g., of 652 AEFI records with a serious outcome, 54.9% had causality ratings of certain or probable, and 91.9% were for children aged <7 years).

TABLE 3 Vaccine types listed as “suspected” in records of AEFI in the NASS database, 2008 to 2011

Suspected vaccine type ^a	Total no. of AEFI records	One suspected vaccine only ^b		Certain/probable causality rating		Serious outcome	
		No. of AEFI records	% of AEFI records ^c	No. of AEFI records	% of AEFI records ^c	No. of AEFI records	% of AEFI records ^c
23vPPV	275	268	97.5	12	4.4	0	0.0
7vPCV	48	48	100.0	0	0.0	0	0.0
BCG	122	103	84.4	27	22.1	26	21.3
DTP	1,833	1,366	74.5	82	4.5	314	17.1
DT	327	311	95.1	48	14.7	137	41.9
Influenza	135	129	95.6	5	3.7	3	2.2
HepA	107	94	87.9	0	0.0	2	1.9
HepB	163	129	79.1	0	0.0	0	0.0
Hib	276	219	79.3	2	0.7	8	2.9
JEV	178	142	79.8	0	0.0	10	5.6
MenCV-a	231	179	77.5	6	2.6	0	0.0
MenCV-ac	151	143	94.7	16	10.6	11	7.3
MM	912	868	95.2	52	5.7	77	8.4
MMR	147	97	66.0	5	3.4	3	2.0
MR	459	363	79.1	17	3.7	7	1.5
pH1N1	539	537	99.6	57	10.6	31	5.8
OPV	134	96	71.6	6	4.5	13	9.7
RV	67	61	91.0	3	4.5	2	3.0
VZV	161	153	95.0	7	4.3	8	5.0
Total	6,265	5,306	84.8	345	5.5	652	10.4

^a Influenza, seasonal influenza virus vaccine; RV, rotavirus live attenuated vaccine; VZV, varicella-zoster virus live attenuated vaccine.

^b AEFI records where only 1 vaccine was suspected of involvement in a reported AEFI.

^c Percentages are calculated for the number of AEFI records where the vaccine was suspected of involvement in the AEFI (e.g., of 1,833 AEFI records listing DTP as the suspected vaccine, 74.5% indicated that it was the only suspected vaccine, 4.5% had certain or probable causality ratings, and 17.1% were defined as serious).

mococcal conjugate vaccine (7vPCV), pH1N1, and MenV-ac were the more common vaccines listed as suspected of being involved in reported AEFI, particularly where only one vaccine was listed as being suspected (Table 4).

Reaction. The distribution and frequency of reactions listed in AEFI records for vaccines received between 2008 and 2011 are shown in Table 4. The most frequently reported AEFI was fever (46.2%; 2,894/6,265), followed by injection site reaction (ISR) (39.4%) and allergic reaction (7.2%). Fever was the most commonly reported individual adverse event following receipt of DTP (43.0%; 1,245/2,894), MM (26.2%), pH1N1 (12.8%), and MR (7.3%), administered alone or in combination with other vaccines. ISR was the most commonly reported individual adverse event following receipt of DTP (35.5%; 877/2,470), 23vPPV (18.2%), DT (16.4%), and *Haemophilus influenzae* type b vaccine (Hib) (11.7%).

The most frequently reported anaphylactic reaction was thrombocytopenic purpura (22.5%; 101/449), followed by angioedema (18.3%), Arthus reaction (18.3%), and allergic rash (16.9%). Anaphylaxis reaction was the most frequently reported individual adverse event following receipt of MM (30.5%; 137/449) and DTP (27.4%). More severe anaphylactic reactions included reports of anaphylactic shock ($n = 28$) and laryngeal edema ($n = 8$), of which 19 reports followed receipt of MM, 11 followed receipt of MenV-ac, 4 followed receipt of Hib, and 2 followed receipt of pH1N1.

New pH1N1 2009 influenza virus vaccine. There were a total of 539 AEFI reports received in 2009 for which pH1N1 was listed as a suspected vaccine (Table 3). The reporting rate was 22.83 per

100,000 doses. The reporting rate of serious AEFI was 1.3 per 100,000 doses. It was the only suspected vaccine in 537 (99.6%) reports; 57 (10.6%) had causality ratings of certain or probable, and 31 (5.8%) were defined as serious. The reporting rate of serious AEFI was highest (1.5 per 100,000 doses) among adult people (aged ≥ 18 to 65 years). The most frequently reported categories of reactions associated with administration of pH1N1 included fever (151/539; 28.0%), ISR (24.7%), and anaphylaxis reaction (11.6%).

There were a total of 2 reports of anaphylactic shock and 2 reports of Guillain-Barre syndrome (GBS), for which the patients were all aged ≥ 18 years. Two cases of anaphylactic shock occurred immediately (less than 30 min) after pH1N1 administration: one was reported to have a history of asthma, and one had known allergies to eggs. Two cases of GBS were reported. One case occurred in a patient with a history of infection and was therefore classified as a coincidental event, and the other case showed no evidence of a cause other than vaccination.

MM campaign in 2010. There were a total of 792 AEFI reports received for the MM campaign in 2010 for which MM was listed as a suspected vaccine. The overall AEFI reporting rate was 34.3 per 100,000 doses, and the reporting rate of serious AEFI was 5.6 per 100,000 doses. It was the only suspected vaccine in 779 (98.4%) reports; 37 (4.7%) reports had causality ratings of certain or probable, and 36 (4.5%) were defined as serious.

The most frequently reported categories of reactions associated with administration of MM included fever (393/792; 49.6%) and ISR (27.2%). A total of 41 (5.2%) anaphylaxis reactions were reported and included allergic rash ($n = 27$), angioedema ($n = 8$),

TABLE 4 Reaction categories of AEFI in the NASS database, 2008 to 2011

Reaction	Total no. of AEFI records	Certain/probable causality rating		Patients <7 yr of age		Patients ≥7 yr of age	
		No. of AEFI records	% of AEFI records ^a	No. of AEFI records	% of AEFI records ^a	No. of AEFI records	% of AEFI records ^a
Fever (temp [°C])							
37.1–37.5	839	312	37.2	715	85.2	124	14.8
37.6–38.5	928	261	28.1	770	83.0	158	17.0
≥38.6	1,127	348	30.9	1,054	93.5	73	6.5
ISR (diam of area of redness and swelling [cm])							
≤2.5	722	349	48.3	694	96.1	28	3.9
2.6–5.0	841	430	51.1	772	91.8	69	8.2
>5.0	907	483	53.3	874	96.4	33	3.6
Anaphylaxis reaction							
Allergic rash	76	28	36.8	64	84.2	12	15.8
Angioedema	82	27	32.9	71	86.6	11	13.4
Anaphylactic shock	28	22	78.6	22	78.6	6	21.4
Henoch-Schonlein purpura	72	20	27.8	61	84.7	11	15.3
Arthus reaction	82	39	47.6	67	81.7	15	18.3
Laryngeal edema	8	8	100.0	6	75.0	2	25.0
Thrombocytopenic purpura	101	62	61.4	82	81.2	19	18.8
Sterile reaction	121	53	43.8	94	77.7	27	22.3
Febrile convulsion	113	26	23.0	93	82.3	20	17.7
Vaccine-associated paralytic poliomyelitis	6	6	100.0	6	100.0	0	0.0
GBS	19	0	0.0	14	73.7	5	26.3
Brachial neuritis	37	8	21.6	22	59.5	15	40.5
Seizure	11	0	0.0	11	100.0	0	0.0
Acute disseminated encephalomyelitis	9	0	0.0	9	100.0	0	0.0
Encephalopathy	5	1	20.0	4	80.0	1	20.0
Encephalitis and meningitis	11	0	0.0	6	54.5	5	45.5
Death	15	1	6.7	15	100.0	0	0.0
Other							
Abnormal crying	26	2	7.7	17	65.4	9	34.6
Malaise	41	5	12.2	32	78.0	9	22.0
Hysteria	22	2	9.1	18	81.8	4	18.2
Syncope	16	5	31.3	14	87.5	2	12.5
Total	6,265	2,498	39.9	5,607	89.5	658	10.5

^a Percentages relate to the number of AEFI records in which the specific reaction term was listed, e.g., of 76 AEFI records listing allergic rash, 36.8% had a causality rating of certain or probable and 84.2% were for children aged <7 years.

Arthus reaction ($n = 5$), and laryngeal edema ($n = 1$). One case of laryngeal edema occurred immediately (less than 15 min) after administration. All the patients recovered well, and there were no reports of death or any sequelae.

DISCUSSION

Clinical vaccine trials usually involve a limited number of study subjects and may not allow detection of rare adverse events. Therefore, postlicensure surveillance of AEFI is an integral part of an immunization program to continuously monitor the safety of

vaccines when routinely used in the general population (9). Here we analyzed 6,265 AEFI records during an extended period of time in Zhejiang province, which is a strength of our study. The overall rate of AEFI (9.2 per 100,000 doses), varying between 4.9 and 12.0 per 100,000 doses in the individual years under study, is at the high range of reports from passive surveillance systems in other countries. Approximately 5 to 7 AEFI reports per 100,000 doses were received by the Vaccine Adverse Event Reporting System (VAERS) in the United States (10). In Germany, a country with a

population similar to that of Zhejiang province and by and large with a similar number of immunizations, 3,329 AEFI were reported passively during 3 years (2001 to 2003) (11). In Australia in 2009, a rate of 14.1 AEFI per 100,000 doses was reported (12). The variation in rates of reported AEFI in these different countries may be explained by variable reporting requirements, case definitions, and settings as well as variable compliance with reporting. There was, however, a large increase in the number of AEFI reports received in 2009 and 2010 compared with other individual years, related mainly to the commencement of the pH1N1 immunization program in September 2009 (pH1N1 contributed to 30.9% of the total AEFI reports) and the MM campaign in 2010 (MM contributed to 34.9% of the total AEFI reports), respectively.

We found that the more populous municipalities had lower reporting rates (e.g., Wenzhou) than the less populous ones (e.g., Quzhou), which has also been observed in the United States and Canada (9, 13). This pattern suggests large differences in the sensitivity of the individual municipal AEFI surveillance systems. This is likely to be related, to some extent, to known differences in notification and case investigation procedures. Further study to evaluate and compare AEFI surveillance methods across municipalities would help to elucidate this.

Only 1% of the total AEFIs were classified as serious, which was lower than rates reported by similar AEFI surveillance systems in other countries such as the United States (15%) (14) and Germany (19%) (11). These differences probably reflect variability in reporting regulations but also point to a bias toward reporting of serious AEFI, which in general have been found to be significantly lower in active surveillance systems and in clinical trials than in passive surveillance systems (15). Moreover, only 0.2% of all AEFI reported in our study were deaths (nearly four deaths per study year), with only one of them having a very likely or certain causal relationship with the precedent immunization. With a total of approximately 7,800 deaths of infants (aged ≤ 1 year) per year in Zhejiang province (5), these single reports do not appear to be of concern.

Several studies have shown higher rates of fever or ISR following receipt of a dose of pertussis-containing vaccines (e.g., DTP) than for other vaccines (16–18), which was consistent with our findings. These reactions may be characteristic of DTP. Despite being extensive, they are usually associated with minimal discomfort, resolve without sequelae, and should not contraindicate further vaccination.

The safety of pH1N1 has been examined closely both internationally and in China. The overall rate and the rate of serious AEFI were similar to results from passive surveillance systems in China (19) and other countries (20–22). The majority of the 593 reports were mild vaccine side effects similar to those identified in prelicensure clinical trials, which included mainly fever and ISR. Although an association between the influenza virus vaccine and GBS was observed in 1976 (23), assessment of current pH1N1 vaccines had found either no association or a higher rate of GBS with 0.85 per million vaccine doses in our study, which is consistent with estimates for seasonal influenza virus vaccine. This rate is also lower than the baseline incidence rate of 0.6 to 1.9 cases per 1 million population in European countries or the estimated risk of 1 case per 1 million doses of seasonal influenza virus vaccines given in the United States (24, 25).

The overall rate of AEFI associated with MM was higher than that associated with the measles attenuated live vaccine (MV) or

the MR campaign conducted at home and abroad (26–28). This may be because the recipients were more likely to report AEFI, as MM was a new vaccine, which was indicated by the increase in the rate of nonserious AEFI while the rate of serious AEFI remained relatively stable. Most of the AEFI reported were relatively mild and self-limited, with fever and SIR being the most commonly reported reactions. There were no reports of anaphylactic shock, laryngeal edema, sequelae, or death. These findings suggest that the MM has a reasonable safety profile.

To classify a causal relationship between immunization and reported AEFI, we used the WHO guidelines for causality assessment of AEFI. In our opinion, some of the categories in this classification guideline are imprecisely defined. Therefore, we modified the classification system to fit our needs. Modifications in our view added clarity to the WHO categories but admittedly were a subjective interpretation on our side. In the future, the establishment of more precise criteria for causality assessment could lead to greater validity and better efficiency.

Limitations and advantages. There are still a number of limitations and strengths regarding this study. As an inherent weakness of passive reporting systems (29, 30), there was significant variability in the quality of reports, potential for biased reporting (leading to underreporting overall), limited power to establish or disprove a causal relationship with immunization in individual reports, and lack of control groups. Our study also has several strengths. First, data have been obtained province wide and over an extended period of time, i.e., 4 years. Second, all AEFI reports were scrutinized in a standardized fashion by provincial CDC investigators. Third, the number of distributed vaccine doses in Zhejiang province was available and allowed calculation of AEFI reporting rates per distributed vaccine doses.

Conclusion. The data reported here illustrate the high level of vaccine safety. The benefits of immunization far outweigh the risks of AEFI, particularly since the majority of those reported are not serious, and many that are serious are only coincidentally associated with immunization.

Despite the acknowledged limitations of a passive surveillance system, the regular analysis and publication of AEFI surveillance data collated in the NASS database remain important aspects of the EPI, and this will serve as a baseline for repeated analyses of this ongoing surveillance in the future. However, to improve the quality of the current system, several modifications should be considered. These may include the collection of more detailed individual clinical data, standardized case definitions, enhancement of follow-up of patients, and establishment of a sentinel system for active surveillance.

ACKNOWLEDGMENTS

We are grateful to all physicians in all health centers for providing AEFI reports in Zhejiang province. We thank our colleagues of CDCs at municipal and county levels for collecting and collating data. We appreciate critical review of the manuscript by Yiming Zhu, School of Public Health, Zhejiang University, Hangzhou, China.

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